

homo-oligomers of [meth-]acrylamide derivatives and co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers and that the biodegradable thermally reversible graft copolymer forms a reversible gel. This amendment was to correct typographical errors that inadvertently recited the species twice and to specify that the copolymer forms a reversible gel. Support for the formation of a reversible gel is found in the title, throughout the specification, and the claims. No new matter is added thereby. Pursuant to rule 121(c)(3), the version of the amended claims to show changes made is submitted in a separate paper enclosed herein.

REMARKS

The Examiner has noted that drawing sheet 2 containing Figure 3 was missing from the Examiner's file. A true and correct copy of drawing sheet 2 has been submitted herewith. The Examiner has acknowledged the Applicant's election of polysaccharides in Paper No. 9. The Applicant herein admits on the record that the species are not patentably distinct. The Examiner indicated in Paper No. 10 that the Applicant's election will be treated as an election without traverse. The Examiner had previously indicated in Paper No. 4 that all claims were generic, and that upon the allowance of a generic claim, the Applicant will be entitled to consideration of claims to additional species which are written in dependant form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. In light of this assurance on the part of the Examiner, the Applicant elected the single species of polysaccharides in Paper No. 9 with traverse. Is it the Examiner's position that the Applicant is not entitled to rely on this assurance of the Patent and Trademark Office in making the election with traverse? The Applicant respectfully requests that the Examiner withdraw the Examiner's restriction.

35 USC 112

The Examiner has rejected claims 1-12 and 31-36 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which the Applicant regards as the invention. The Examiner queries whether the "hydrophilic comonomer" is optional. The Applicant has amended Claim 1 and (claims 2-12 by virtue of dependency) to recite the limitation that the hydrophilic comonomer in the linear random copolymer is less than about 10 mole% and greater than or equal to about 1 mole%, thus requiring the presence of the hydrophilic comonomer. The Applicant respectfully requests that the Examiner withdraw this objection. The Examiner has further noted an ambiguity with respect to the Markush group of Claim 31. Claim 31 (and claims 32-36 by virtue of dependency) have been amended to recite that the side chains are selected from the group consisting of homo-oligomers of [meth-]acrylamide derivatives and co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers, thus removing the ambiguity. The Applicant respectfully requests that the Examiner withdraw the Examiner's restriction.

35 USC 102 (b) and 35 USC 103 (a)

The Examiner has rejected claims 1-11 under 35 USC 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as obvious over Sassi et al. (USP 5,631,337). The Examiner's attention is thus drawn to the requirement that the carrier of claim 1, and claims 2-11 by virtue of dependency, contain the limitation that the carrier contain a hydrophilic comonomer in the linear random copolymer. The inclusion of this hydrophilic comonomer insures that the carrier claimed by the Applicant is separate and distinct from the Sassi disclosure, and refutes the Examiner's assertion that the Sassi reference discloses all the limitations of the claim, and that the property or function of the absence of synerisis is therefore inherent.

In fact, the inclusion of this hydrophilic comonomer insures that the carrier claimed by the Applicant operates in a manner precisely opposite to that disclosed by Sassi. In Sassi, the polymers are linear and non ionic. In contradistinction, the carrier claimed by the Applicant is ionic. Sassi's polymer

gels upon cooling (see column 5, line 65) whereas the carriers claimed by the Applicant gel upon heating. In Sassi, gelation occurs as a result of the formation of hydrogen bonds brought about by cooling (see claim 1) whereas the carriers claimed by the Applicant are hydrogen bonded to water in a non-gelled state, and then when heated, the hydrogen bonds are disrupted and the N-isopropyl groups gel by hydrophobic interactions. Accordingly, the gelation of the Sassi polymers utilize the exact opposite mechanism of the carriers claimed by the Applicant.

In light of the Applicant's inclusion of the limitation that the carrier contain a hydrophilic comonomer in the linear random copolymer, the Sassi disclosure cannot possibly support a prima facie case of anticipation under 35 USC 102(b) as it is axiomatic that a proper rejection under 35 U.S.C. 102 must contain each and every limitation of the claim, ("[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration" W.L. Gore & Assocs. V. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983). With respect to a rejection under 35 USC 103(a), "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." Ex parte Clapp, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In light of the Applicant's inclusion of the limitation that the carrier contain a hydrophilic comonomer in the linear random copolymer, the Sassi disclosure cannot possibly "expressly or impliedly suggest the claimed invention" since the Sassi disclosure makes no mention whatsoever of this limitation, and in fact operates in a manner completely opposite to that taught by this limitation.

With respect to claims 2-11, the Examiner has completely failed to set forth a prima facie case of anticipation under 35 USC 102(b) or 35 USC 103(a) with or without this additional limitation. The Examiner has failed entirely to

address how the Sassi disclosure relates to any of the additional limitations provided in each of these dependant claims. As stated by the Federal Circuit, "[t]he Examiner cannot sit mum, leaving the applicant to shoot arrows in the dark hoping to somehow hit a secret objection harbored by the examiner. The 'prima facie' case notion... was intended to leave no doubt among examiners that the must state clearly and specifically any objections (the prima facie case) to patentability, and give the applicant fair opportunity to meet those objections with evidence and argument. To that extent the concept serves to level the playing field and reduces the likelihood of administrative arbitrariness." In re Oetiker, 977 F.2d 1443, 24 USPQ 2d 1443, 1447 (Fed. Cir. 1990) (Plager, J., concurring). The Applicant respectfully requests that the Examiner either address the additional limitations in dependant claims 2-11, or withdraw the Examiner's rejection under 35 USC 102(b) and 35 USC 103(a) on the basis of the Sassi disclosure.

The Examiner has rejected claims 1-12 under 35 USC 102(b) as being anticipated by, or in the alternative, under 35 USC 103(a) as obvious over Bae et al. (USP 5,262,055). The Examiner's attention is thus drawn to the requirement that the carrier of claim 1, and claim s 2-12 by virtue of dependency, contain a hydrophilic comonomer in the linear random copolymer. The inclusion of this hydrophilic comonomer insures that the carrier claimed by the Applicant is separate and distinct from the Bae disclosure, and refutes the Examiner's assertion that the reference discloses all the limitations of the claim, and that the property or function of no synerisis is therefore inherent.

In fact, synerisis of the polymer in the Bae disclosure is explicit. At column 10, lines 41-50, Bae explicitly discloses

This suspension will be injected... and the polymer **14** will collapse... as the temperature is raised to or above the LCST. Decreasing the temperature will solubilize the collapsed matrix.

As pointed out in the Applicant's Preliminary Remarks, filed January 14, 1999, the reason that the polymer or matrix collapses is the result of the

expulsion of water, or syneresis, upon gelation. Accordingly, the Bae disclosure is readily distinguished from the now pending claims, as Bae specifically discloses that which the now pending claims specifically restrict. Further, in light of the differences in the carrier claimed by the Applicant and the polymers disclosed by Bae, this property cannot properly be termed "inherent" in the claimed subject matter, particularly since Bae explicitly discloses this property.

In light of the Applicant's inclusion of the limitation that the carrier contain a hydrophilic comonomer in the linear random copolymer, the Bae disclosure cannot possibly support a prima facie case of anticipation under 35 USC 102(b) as it is axiomatic that a proper rejection under 35 U.S.C. 102 must contain each and every limitation of the claim, ("[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration" *W.L. Gore & Assocs. V. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983). With respect to a rejection under 35 USC 103(a), "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). In light of the Applicant's inclusion of the limitation that the carrier contain a hydrophilic comonomer in the linear random copolymer, and that the gelation occurs with substantially no syneresis, the Bae disclosure cannot possibly "expressly or impliedly suggest the claimed invention" since the Bae disclosure makes no mention whatsoever of the first limitation, and in fact explicitly sets forth an operation that is opposite of the second limitation.

With respect to claims 2-12, the Examiner has again completely failed to set forth a prima facie case of anticipation under 35 USC 102(b) or 35 USC 103(a) with or without the additional limitation added with these amendments. The Examiner has failed entirely to address how the Bae disclosure relates to any of the additional limitations provided in each of these dependant claims.

The Applicant respectfully requests that the Examiner either address the additional limitations in dependant claims 2-12 or withdraw the Examiner's rejection under 35 USC 102(b) and 35 USC 103(a) on the basis of the Bae disclosure.

Finally, the Examiner has rejected claims 1-12 and 31-36 under 35 USC 102(e) as being anticipated by, or in the alternative, under 35 USC 103(a) as obvious over Hoffman et al. (USP 5,998,588). With respect to claims 1-12, the Examiner has completely failed to set forth a prima facie case of anticipation under 35 USC 102(e) or obviousness under 35 USC 103(a). The Examiner has failed entirely to address how the Hoffman disclosure relates to any of the limitations provided in claims 1-12, and claims 32-36 and has instead limited his reasons for rejection to Claim 31. Again, as set forth by the Federal Circuit, "[t]he Examiner cannot sit mum, leaving the applicant to shoot arrows in the dark hoping to somehow hit a secret objection harbored by the examiner. The 'prima facie' case notion... was intended to leave no doubt among examiners that the must state clearly and specifically any objections (the prima facie case) to patentability, and give the applicant fair opportunity to meet those objections with evidence and argument. To that extent the concept serves to level the playing field and reduces the likelihood of administrative arbitrariness." In re Oetiker, 977 F.2d 1443, 24 USPQ 2d 1443, 1447 (Fed. Cir. 1990) (Plager, J., concurring). Accordingly, the Applicant is at a loss to explain how the Examiner could have possibly concluded that the Hoffman disclosure forms a prima facie case of obviousness or anticipation with respect to claims 1-12, or with regard to the additional limitations set forth in dependant claims 32-36. The Applicant respectfully requests that the Examiner either address independent claim 1 and the additional limitations in dependant claims 2-12 and 32-36, or withdraw the Examiner's rejection under 35 USC 102(b) and 35 USC 103(a) on the basis of the Hoffman disclosure.

Failing such an explanation, the Examiner's attention is again drawn to the requirement that the carrier of claim 1, and claims 2-12 by virtue of

dependency, contain a hydrophilic comonomer in the linear random copolymer. As the Hoffman disclosure fails to disclose a hydrophilic comonomer, Hoffman cannot form a prima facie case of obviousness or anticipation with respect to claims 1-12. Further, with respect to claims 31-36, the Examiner's attention is drawn to the Applicant's inclusion of the limitation that the biodegradable thermally reversible graft copolymer form a reversible gel. In including this limitation, the Applicant has made plain that a central characteristic of the present invention is that a reversible gel is formed. In contrast, the Hoffman disclosure does not remotely disclose or suggest a gel. Rather, Hoffman discloses a conjugate that precipitates from a solution in response to temperature change to form a colloidal suspension. Hoffman does so because the Hoffman disclosure is directed to methods for chemical separations, as opposed to methods for forming gels. Hoffman cannot therefore form the basis for a prima facie case of anticipation as ("[a]nticipation requires the disclosure in a single prior art reference of each element of the claim under consideration" *W.L. Gore & Assocs. V. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983) and Hoffman is missing the element of forming a gel.

Hoffman's concern with methods for chemical separations also insures that Hoffman cannot form the basis for a prima facie case of obviousness under 35 USC 103(a), "To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). Since Hoffman neither expressly or impliedly suggests the formation of a reversible gel, Hoffman cannot form the basis for a prima facie case of obviousness under 35 USC 103(a).

With respect to the Examiner's argument that the Hoffman reference discloses all of the limitations of a claim except a property or function, the Applicant notes that the Hoffman reference specifically discloses the formation

of a conjugate that forms as a precipitate, and that Hoffman doesn't disclose the formation of a gel. Unless the Examiner is taking the position that Hoffman's precipitate is actually a gel, a position that would force the Examiner to not only disregard the explicit teaching of the very reference upon which the Examiner relies and also to conclude that all copolymers necessarily form gels, the Examiner cannot conclude that gelation is an inherent property of the materials and methods disclosed in the Hoffman reference. Quoting from the MPEP "[w]hen an examiner relies on a scientific theory, evidentiary support for the existence and meaning of that theory *must be provided*. In re Grose, 592 F.2d 1161, 201 USPQ 57 (CCPA 1979) see In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420-421 (CCPA 1970) ('[A]ssertions of technical facts in areas of esoteric technology *must always be supported by citation of some reference work*' and 'allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art *should also be supported*.' Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations. 'The facts so noticed serve to 'fill the gaps' which might exist in the evidentiary showing" and *should not comprise the principle evidence upon which a rejection is based.*') (italics added). Thus, if the Examiner wishes to conclude that despite its explicit teaching to the contrary, the methods of Hoffman in fact form a gel, the Examiner is hereby requested to supply extrinsic evidence to support that conclusion, or to avoid relying on that conclusion as the principle evidence upon which the Examiner's rejection now rests.

Further, the Examiner's attention is drawn to the Federal Circuit's decisions in regarding inherency. For a claim to be inherent in the prior art it "is not sufficient that a person following the disclosure *sometimes* obtain the result set forth in the [claim]; *it must invariably happen*." (emphasis added). Standard Oil Co. (Indiana) v. Montedison, S.p.A., 664 F.2d 356, 372, 212 USPQ 327, 341 (3d Cir. 1981), cert. Denied, 456 U.S. 915, 215 USPQ 95(1982). "To serve as an anticipation when the reference is silent about the asserted inherent

characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is *necessarily* present in the thing described in the reference and *that it would have been recognized by persons of ordinary skill.*" (emphasis added).

Continental Can Co. USA v. Monsanto Co., 948 F.2d 1264, 20 USPQ 2d 1746, 1749-50 (Fed. Cir. 1991). If the Examiner is of the opinion that, contrary to the explicit teaching of Hoffman, the materials and methods of Hoffman will *necessarily* form a gel, the Applicant respectfully requests that the Examiner set forth extrinsic evidence supporting that conclusion.

Absent such extrinsic evidence, the Applicant respectfully requests that the Examiner withdraw the Examiner's rejection of all pending claims under 35 USC 102(b) and 35 USC 103(a) on the basis of the Hoffman disclosure.

Closure

Applicant has made an earnest attempt to place the above-referenced application in condition for allowance and action toward that end is respectfully requested. In the alternative, the Applicant respectfully requests that the Examiner enter the foregoing amendments to place the Application in better form for appeal. Should the Examiner have any further observations or comments, he is invited to contact the undersigned for resolution.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gutowska) Art Unit: 1711
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Serial No: 09/209,541) Examiner: Jeffrey Mullis
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Filed: 12/11/98) Paper No: 11
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Assistant Commissioner for Patents
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Version of Amended Claims to Show Changes Made

Claims 1 and 31 were amended as follows where underlined matter was inserted and {bracketed} matter deleted:

1. (amended) A therapeutic agent carrier, comprising:
 - a. a reversible gelling copolymer, having a linear random copolymer of:
 - i. an N-alkyl substituted [meth-]acrylamide derivative; and
 - ii. a hydrophilic comonomer, wherein an amount of said hydrophilic comonomer in the linear random copolymer is less than about 10 mole% and greater than or equal to about 1 mole% wherein gelation occurs with substantially no syneresis, said linear random copolymer in the form of a plurality of linear chains having a plurality of molecular weights greater than or equal to a minimum gelling molecular

weight cutoff, and excluding a substantial amount of copolymer chains or polymer chains having molecular weights less than the minimum gelling molecular weight cutoff;

- b. an aqueous solvent mixed with said reversible gelling copolymer as a reversible gelling solution; and
- c. a therapeutic agent mixed with said reversible gelling solution as said therapeutic agent carrier.

31. (amended) A biodegradable thermally reversible graft copolymer, comprising:

- d. a biodegradable polymer; grafted with
- e. a side chain selected from the group consisting of homo-oligomers of [meth-]acrylamide derivatives and {co-oligomers of [meth-]acrylamide derivatives homo-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers,} co-oligomers of [meth-]acrylamide derivatives copolymerized with hydrophilic comonomers,
- f. said biodegradable thermally reversible graft copolymer forming a reversible gel.